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ART UNIT	PAPER NUMBER
1644	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/290,029	BOTTOMLY ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

-- The MAILING DATE of this communication app ars on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 50-55,60,61,63-69,79-98,102-112,115-117,122,123,125-127,129,136-157,160-176 and 184-193.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 61,67-69,82,92,98,105-107,117,127,140,151,157,176,186,192 and 193.

Continuation of Disposition of Claims: Claims rejected are 50-55,60,63-66,79-81,83-91,93-97,102-104, 108-112,115,116,122,123,125,126,129,136-139,141-150,152-156,160-175,184,185 and 187-191.

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Megan Jamroz, Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 4/9/2001 (Paper No. 13), is acknowledged.

Claims 50-55, 60, 61, 63-69, 79-98, 102-112, 115-117, 122-123, 125-127, 129, 136-157, 160-176 and 184-193 are pending.

Claims 61, 67-69, 82, 92, 98, 105-107, 117, 127, 140, 151, 157, 176, 186, and 192-193 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to non-elected species of Group XIV.

Claims 50-55, 60, 63-66, 79-81, 83-91, 93-97, 102-104, 108-112, 115-116, 122-123, 125-126, 129, 136-139, 141-150, 152-156, 160-175, 184-185, and 187-191 read on the elected species of the elected invention and are being acted upon, wherein the elected invention comprises a method of modulating an immune system response to an antigen away from a Th2 response comprising isolating one or more pAPC from an individual and exposing said pAPC to an inducing agent factor concurrently with exposure to a protein antigen then administering said pAPC to a subject, said elected species consisting of:
(a) pAPC – dendritic cell,
(b) factor – CpG (Th1 inducing agent),
(c) antigen – crude antigen preparation,
(d) targeting agent – Fc receptor ligand (FcRL), mannose receptor ligand, and DEC-205, and
(e) encapsulating device – liposome.

3. The disclosure is objected to because of the following informalities: the specification fails to provide support for the limitations in claims 80, 97, 138, 156, 184, and 191 wherein the association occurs through a type of bond or combination thereof.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, 108-109, 111-112, 122-123, 125-126, 129, 136-150, 153-156 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in Paper No. 11, mailed 12/6/2000.

6. Claim 50 recites the limitation "allergic antigen" in line 5, and claim 109 recites the limitation "allergic antigen" in line 4. There is insufficient antecedent basis for this limitation in the preamble of the claims. It is suggested that the antigen in claim 50, line 2 be changed to "allergen", and in claim 109, line 1, be changed to "allergen".

7. Claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, 108-112, 115-116122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps for the same reasons set forth in Paper Nos. 7 and 11. See MPEP § 2172.01. The omitted steps are: (1)administering isolated and exposed pAPC to a subject so as to modulate an immune response, and (2) concurrent exposure of the pAPC to the CpG oligonucleotides prior to administration to a subject so as to modulate an immune response.

Applicant's arguments filed, 4/9/2001, have been fully considered but they are not found persuasive.

Applicant argues that the "immune system" is defined in the specification such that it can refer to an *in vivo* or an *in vitro* response, that primary immune response is defined as referring to the initial activation of "immune system" cells when they encounter or recognize a particular antigen for the first time. Further, applicant argues that on page 24, line 5 of the specification, modulation *ex vivo* is discussed and provides ample support such that an essential step is not omitted. Finally, applicant argues that the Janeway et al. textbook does not limit "immune system" to *in vivo* systems and that applicant can act as his own lexicographer as long as the meaning of the word is not repugnant to the usual meaning of the term.

(1) It is the examiner's position that an essential step has been omitted as described supra. Specifically, the examiner believes that if an immune system response is to be "modulated", the cytokines produced must be present in the individual in order to actually have the "modulation" (i.e. to switch to a Th1 response) occur. Indeed, production of a set of cytokines alone does not have the effect of modulation if they do not then act upon another set of cells within the immune system to cause a switch from a Th2 response to a Th1 response. Therefore, the exposed and isolated pAPC must be administered to a subject so that the cytokines can act on their respective target cells.

The examiner believes that the usual meaning of the term "immune system" according to sources such as Janeway et al. (Immunobiology: The Immune System in Health and Disease, Current Biology Ltd. London, 1994, pages 1 and I:10), is that the "system" is a collection of organs, tissues, cells, and molecules, or sometimes the totality of host defense mechanisms (see page 1, line 1 and the definition of immune system on page i:10 in particular). Further Merriam-Webster's Dictionary (10th ed. Merriam-Webster, Inc. Springfield, 1996, page 508) specifically defines an "immune response" as a **bodily** response to an antigen …" and an "immune system" as a **bodily system** that protects the body from foreign substances, cells, and tissues by producing the immune response and that includes especially, the thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract, and bone marrow), lymphocytes including the B cells and T cells and antibodies (see page 580 in particular). With respect to applicant's arguments regarding the ex vivo modulation disclosed on page 24, lines 5-14 of the specification, applicant describes only exposure of antigen to pAPC to favor uptake and presentation of the antigen in a manner likely to bias a subsequent response by helper T cells that come into contact with the pAPC. It is the examiner's position that this description does not support the use of *in vitro* organ or tissue cultures, only

helper T cells; thus, it is the examiner's position that in view of two highly respected sources that define "immune system" and "immune response" as discussed supra, the art recognized definitions of "immune system" and "immune response" encompass an *in vivo* response and the disclosure on page 24, line 5 is not sufficient to overcome the art-recognized definitions. Therefore, the method of modulating an immune system response to an antigen as claimed would require administering isolated and exposed pAPC to a subject so as to modulate an immune response *in vivo*.

In regard to applicant's arguments that a primary immune response that the immune response can take place *in vitro*, the claims are drawn to modulating an immune system response to an antigen wherein the endpoint is generation of a pre-determined set of cytokines. It is the examiner's opinion that in order for the "immune system", as defined by Janeway et al. and the Merriam-Webster's Dictionary supra, to be "modulated" the cytokines must act on their target immune cells, therefore, the isolated and exposed pAPC (such as those in claim 50, for example) must be administered to a patient. In the instant case, generation of Th1 cytokines to modulate away from a Th2 response includes cytokines such as IL-12 and IFN-γ which would be required to act upon other cell types such as, NK cells and B cells, respectively to reach a final endpoint of modulating an immune system away from a Th2 response as taught by Arthur Krieg (BioDrugs, 1998; 10(5): 341-346).

(2) With respect to the omission of the essential step of concurrently exposing the pAPC to allergen and the CpG oligonucleotide, in the absence of the CpG oligonucleotide, the immune response would be driven toward a Th2 response, rather than away from it. The presence of the CpG oligonucleotide is essential to cause the shift away from a Th2 response toward a Th1 response.

Further, with respect to dependent claim 108, independent claim 50 does not include concurrently treating the pAPC with CpG to switch to a Th1 cytokine response or administering the isolated and exposed pAPC to a patient. Therefore, if the pAPC are isolated and exposed, but NOT administered to a patient, and the allergen is administered to a subject as recited in claim 108, the allergen would drive a Th2 response.

8. Claims 50, 109, and 160 are indefinite and ambiguous in the recitation of "allergic antigen". It is recommended that the claims be amended to recite the art recognized term of "allergen".

9. Claim 53 is indefinite and ambiguous in the recitation of "wherein the antigen-exposed pAPC are immature" pAPC. If the dendritic cells have been exposed to antigen, they have gone through a maturation process and can no longer be immature.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, 108-112, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-164, 169, 171-175, 184-185, and 188-191 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating an immune response to an antigen away from a Th2 response comprising isolating one or more dendritic cells (pAPC) from an individual and concurrently exposing said pAPC to an allergen, a CpG oligonucleotide (an inducing agent factor), and a FcRL (targeting agent) then administering said "isolated and exposed" pAPC to a subject to modulate the immune response away from a Th2 response, does not reasonably provide enablement for a method of modulating an immune response to an antigen away from a Th2 response comprising isolating one or more dendritic cells (pAPC) from an individual and exposing said pAPC to an allergen and/or FcRL (targeting agent) then administering said pAPC to a subject to modulate the immune response away from a Th2 response in the absence of the CpG oligonucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

It is well known in the art that allergens drive Th2 responses (i.e. IgE). Galli et al. (Fundamental Immunology, 4th ed. Lippencott-Raven, Philadelphia, 1999, pages 1131, 1135, and 1147) that allergens exposed to and presented by dendritic cells drive IgE production in Th2 cell-driven responses (see the figures on pages 1131 and 1135, and page 1147, right column, paragraph 3 in particular).

Therefore, in the absence of the CpG oligonucleotide (an inducing agent factor), the response would be driven **toward** a Th2 response rather than away from a Th2 response. The combination of all three ingredients (i.e. the allergen, the CpG oligonucleotide (an inducing agent factor), and the Fc receptor ligand (targeting agent)) must be concurrently exposed to the dendritic cell (pAPC) to achieve the endpoint of modulating the immune response of a patient away from a Th2 response following administration of the isolated and exposed dendritic cells (pAPC).

Consequently, applicant has not taught one skilled in the art how to make or use an isolated dendritic cell (pAPC) exposed to an allergen and/or FcRL (targeting agent), to modulate an immune response of a patient away from a Th2 response in the absence of the CpG oligonucleotide (Th1 inducing factor). The CpG oligonucleotide is the critical signal that is strong enough to turn off the Th2 response to switch to a Th1 response (i.e. "modulate" away from a Th2 response).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 50-55, 60, 109, 111-112, and 126 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 5,994,126, of record.

The '126 patent has been discussed in Paper No. 11, mailed 12/6/2000 and Paper No. 7, mailed 6/21/2000. Specifically, the '126 patent teaches a method of modulating an immune system response to an antigen comprising isolating pAPC (e.g. dendritic cells) from an individual and exposing said pAPC to a crude antigen followed by administering said pAPC to a subject (see column 5 last paragraph – column 6 first paragraph; column 6, paragraph 10; and Example 4 in particular). The '126 patent further teaches that the antigen can be an allergen (see column 20, lines 40-41 in particular). Claims 60 and 109 are included because although the '126 patent is silent regarding whether the antigen/allergen is a crude antigen preparation, the examiner is interpreting the reference as such because the '126 patent does not teach purification of the antigen prior to exposure of the pAPC. Claim 109 is included because when the "isolated and exposed" pAPC are administered to a subject, inherently, they will contact T cells within the blood and tissues of the subject so that a pre-determine T cell response is inhibited. Claim 53 is included because the examiner is interpreting the claim to mean that the dendritic cells (pAPC) are immature at the moment prior to antigen exposure.

Therefore, the '126 patent anticipates the claimed invention.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 50, 87, and 145 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/33520, (IDS reference, of record).

The '126 patent has been discussed supra.

The '126 patent does not teach encapsulation of the antigen/allergen in a liposome.

The WO 98/33520 document teaches the use of liposomes as "encapsulating devices" for antigens to increase their potency and clinical effectiveness (see page 6, paragraph 3; and page 7, lines 8 and 24 in particular). Further, the WO 98/33520 document teaches that liposomes can deliver exogenous antigen(s) into the endocytic pathway (i.e. intracellular vesicles) of antigen processing and presentation (see page 3, lines 1-19 in particular). The antigen encapsulated in the liposomes has beneficial features in that is delivered to the antigen presenting cell, such as a dendritic cell, and is presented on the cell surface (see page 6, paragraph 3 in particular). More importantly, the WO 98/33520 document teaches that a mixture of immunomodulators can be encapsulated within the liposomes as well (see page 7, paragraph 2 in

particular) and that the composition as a whole allows administration of lower doses of the individual components to have a greater effect (see page 8, lines 21-22 in particular). Finally, the WO 98/33520 document teaches that "administering the immunomodulator in a vehicle containing the antigen both prolongs its half-life and delivers it in close proximity to the vaccine or antigen" (see page 9, lines 11-13 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposomes taught by the WO 98/33520 document to encapsulate the antigen/allergen taught by the '126 patent to target the antigen to the antigen presentation pathway of antigen processing cells to modulate an immune response as taught by the '126 patent.

One of ordinary skill in the art would have been motivated to encapsulate the antigen/allergen taught by the '126 patent in a liposome as taught by the WO 98/33520 document to target the antigen/allergen to the endocytic pathway of antigen presenting cells, increase the half-life of the antigen/allergen, and lower the administration dose with a greater effect as taught by the WO 98/33520 document to increase uptake of the antigen/allergen by the dendritic cells to modulate an immune response as taught by the '126 patent with a reasonable expectation of success.

17. Claims 90-91, 94-96, 149-150, and 153-155 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/33520, of record, as applied to claims 50, 87, and 145 above, and further in view of Maurer et al., of record.

The '126 patent and the WO 98/33520 document have been discussed supra.

The combined references do not teach using targeting agent.

Maurer et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome taught by the WO 98/33520 document to encapsulate the antigen/allergen taught by the '126

patent, and the targeting agent taught by Maurer et al. in the method taught by the '126 patent to modulate an immune response away from a Th2 response. Claim 89 is included because placing the antigen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the encapsulated antigen/allergen and targeting agent in the method taught by the '126 patent to modulate an immune response because the liposome increased the half-life of the antigen (with an added benefit of decreased concentration), and the targeting agent would target the CpG motif and antigen/allergen to the endocytic pathway with a reasonable expectation of success.

18. Claims 50, 63, 136, 139, and 142-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Maurer et al., of record.

The '126 patent has been discussed supra.

The '126 patent does not teach using a targeting agent, such as FcRL.

Maurer et al. teach that FcR ligands can facilitate the uptake of antigen by a dendritic cell (see page 176, paragraph 4 in particular). Further, Maurer et al. teach that IgG complexed antigens which bind to FcR on dendritic cells (i.e. FcRL); amnnosylated/fucosylated antigens which bind to mannose receptors on dendritic cells (i.e. targeting agent to mannose receptors); and only in rodents, targeting of specific glycosylation patterns on proteins to a C-type lectin receptor, DEC-205; all three of which are involved in the selective uptake and presentation of certain pathogens (see page 175, page 126, lines 1-3 in particular). The Maurer et al. reference also teaches implications for treatment of allergy, and that FcR-IgE dependent allergen uptake by dendritic cells "may both quantitatively and qualitatively modulate allergen presentation *in vitro* and may have profound implications on the magnitude and diversification of allergen-specific T cell responses in human disease" (see page 177, final 3 lines in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the FcRL taught by Maurer et al. to act as a targeting agent for the antigen/allergen taught by the '126 patent to modulate an immune response, such as allergic responses as taught by Maurer et al. Claims 142-144 are included because the entire IgG molecule taught by Maurer et al. is encompassed within the meaning of "at least the Fc portion of an Ig molecule" as recited in claim 143, and "at least the Fc portion of an IgG molecule" as recited in claim 144.

One of ordinary skill in the art would have been motivated to use an Ig-antigen/allergen complex taught by Maurer et al. to target the antigen/allergen to antigen processing cells, such as dendritic cells, as taught by both the '126 patent and Maurer et al. to modulate an immune response, such as allergy, for therapeutic purposes with a reasonable expectation of success.

19. Claims 80 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Maurer et al., of record, as applied to claims 50, 63, 136, 139, and 142-144 above, and further in view of Davies et al. (PNAS 1996; 93: 7-12).

The '126 and Maurer et al. references have been discussed supra.

The combined references do not teach association of the antigen and the targeting agent by bonds, such as those recited in claim 138.

Davies et al. teach that antigens and antibodies interact through hydrogen bonds at the site of interaction (see the Abstract in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the FcRL taught by Maurer et al. to act as a targeting agent for the antigen/allergen taught by the '126 patent to modulate an immune response, such as allergic responses as taught by Maurer et al. Claims 142-144 are included because the entire IgG molecule taught by Maurer et al. is encompassed within the meaning of "at least the Fc portion of an Ig molecule" as recited in claim 143, and "at least the Fc portion of an IgG

molecule" as recited in claim 144. It would have further been obvious to one of ordinary skill in the art at the time the invention was made that the IgG and antigen/allergen were acting via hydrogen bonds as taught by Davies et al.

One of ordinary skill in the art would have been motivated to use an Ig-antigen/allergen complex taught by Maurer et al. to target the antigen/allergen to antigen processing cells, such as dendritic cells, as taught by both the '126 patent and Maurer et al. to modulate an immune response, such as allergy, for therapeutic purposes with a reasonable expectation of success.

20. Claims 50, 60, and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of U.S. Patent 5,994,126, of record.

The '126 patent has been discussed supra.

The '126 patent does not specifically teach that the antigen is a crude antigen preparation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a crude antigen presentation in the method taught by the '126 patent because a crude preparation of the antigen/allergen would have a greater number of epitopes to be presented by the pAPC. Claims 60 and 126 are included because the absence of purification to a more pure product indicates that the antigen/allergen was a crude antigen preparation.

One of ordinary skill in the art would have been motivated to use a crude antigen preparation of an antigen/allergen in the method taught by the '126 patent because a greater number of epitopes would be presented by the pAPC allowing for a greater modulation of the immune system with a reasonable expectation of success.

21. Claims 50, 63-66, 102-104, 115-116, 122-125, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/37919, of record.

The '126 patent has been discussed supra.

The '126 patent does not teach the modulation of the immune response away from a Th2 response (i.e. toward a Th1 response) and the generation of a specific set of cytokines (Th1), nor does it use a "factor", such as a CpG motif, with the antigen when exposing the pAPC to said antigen.

WO 98/37919 teaches that an immune response can be redirected away from a Th2 response by directing it towards a Th1 response with the concurrent generation of a specific set of Th1 type cytokines (see page 4, paragraph 3 in particular). The reference also teaches the use of a CpG motif for the specific directing of a Th2 type immune response towards a Th1 type immune response and that the Th1 subset promotes delayed type hypersensitivity and cell-mediated immunity. Further the reference teaches the use of said method for the treatment of a disease or condition that would benefit from the redirection of an immune response (see page 19, lines 11-21 and page 19, paragraphs 1-2 in particular). One of the diseases that would benefit from said treatment is asthma (i.e. a Type I allergic disease caused by allergens; see page 1, paragraph 3 in particular). The invention as taught by the WO 98/37919 document includes a method of redirecting a subject's immune response from a Th2 to a Th1 response by inducing monocytic (pAPC) and other cells to produce (i.e. express) Th1 cytokines (see page 4, paragraph 2 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the CpG motif to cause pAPC to express Th1 cytokines as taught by the WO 98/37919 document in the method taught by the '126 patent to modulate an immune response away from a Th2 response.

One of ordinary skill in the art would have been motivated to use the CpG motif to modulate an immune response away from a Th2 response as taught by the WO 98/37919 document in the method taught by the '126 patent because it is a useful treatment modality for Type I allergic diseases as taught by the WO 98/37919 document with a reasonable expectation of success.

22. Claims 79, 81, 84-86, 137, 139, and 142-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/37919, of record, as applied to claims 50, 63-66, 102-104, 115-116, 122-125, and 129 above, and further in view of Maurer et al., of record.

The '126 patent and the WO 98/37919 document have been discussed supra.

The combined references do not teach using a targeting molecule to target the antigen/allergen to the pAPC.

The Maurer et al. reference has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the FcRL taught by Maurer et al. with the CpG oligonucleotide as taught by WO 98/37919 to act as a targeting agent for the antigen/allergen taught by the '126 patent to modulate an immune response, such as allergic responses as taught by Maurer et al, and to modulate the immune response toward a Th1 response as taught by WO 98/37919. Claims 142-144 are included because the entire IgG molecule taught by Maurer et al. is encompassed within the meaning of "at least the Fc portion of an Ig molecule" as recited in claim 143, and "at least the Fc portion of an IgG molecule" as recited in claim 144.

One of ordinary skill in the art would have been motivated to use an Ig-antigen/allergen complex taught by Maurer et al. with the CpG oligonucleotide as taught by WO 98/37919 to target the antigen/allergen to antigen processing cells, such as dendritic cells, as taught by both the '126 patent and Maurer et al. to modulate an immune response away from a Th2 response and toward a Th1 response, and because it is a useful treatment modality for Type I allergic diseases as taught by the WO 98/37919 document with a reasonable expectation of success.

23. Claims 88-89, and 146-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/37919, of record, as applied to claims 50, 63-66, 102-104, 115-116, 122-125, and 129 above, and further in view of WO 98/33520, of record.

The '126 patent and the WO 98/37919 document have been discussed supra.

The combined references do not teach using an encapsulating devise.

The WO 98/33520 document has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome taught by the WO 98/33520 document to encapsulate the CpG motif taught by the WO 98/37919 document and the antigen/allergen taught by the '126 patent in the method taught by the '126 patent to modulate an immune response away from a Th2 response. Claim 89 is included because placing the antigen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the encapsulated antigen/allergen and CpG motif to modulate an immune response away from a Th2 response as taught by the WO 98/37919 document in the method taught by the '126 patent because it is a useful treatment modality for Type I allergic diseases as taught by the WO 98/37919 document, and the liposome increased the half-life of the antigen with an added benefit of decreased concentration with a reasonable expectation of success.

24. Claims 83, 90-91, 93-96, 141, 149-150, and 152-155 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/37919, of record, as applied to claims 50, 63-66, 102-104, 115-116, 122-125, and 129 above, and further in view of Maurer et al., of record, and WO 98/33520, of record.

The '126 patent and the WO 98/37919 document have been discussed supra.

The combined references do not teach using an encapsulating devise or using a targeting molecule to target the antigen/allergen to the pAPC.

The Maurer et al. and WO 98/33520 references have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome taught by the WO 98/33520 document to encapsulate the CpG motif taught by the WO 98/37919 document, the antigen/allergen taught by the '126 patent, and the targeting agent taught by Maurer et al. in the method taught by the '126 patent to modulate an immune response away from a Th2 response. Claim 89 is included because placing the antigen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the encapsulated antigen/allergen, CpG motif, and targeting agent to modulate an immune response away from a Th2 response as taught by the WO 98/37919 document in the method taught by the '126 patent because it is a useful treatment modality for Type I allergic diseases as taught by the WO 98/37919 document, the liposome increased the half-life of the antigen (with an added benefit of decreased concentration), and the targeting agent would target the CpG motif and antigen/allergen to the endocytic pathway with a reasonable expectation of success.

25. Claims 97 and 156 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of WO 98/37919, of record, as applied to claims 50, 63-66, 102-104, 115-116, 122-125, and 129 above, and further in view of Maurer et al., of record, WO 98/33520, of record, Merriam-Webster's Dictionary (10th ed. Merriam-Webster, Inc. Springfield, 1996, page 1306), and Davies et al. (PNAS 1996; 93: 7-12).

The '126 patent and the WO 98/37919 document have been discussed supra.

The combined references do not teach using an encapsulating devise or using a targeting molecule to target the antigen/allergen to the pAPC, or specific types of bonds by which the antigen and factor are associated by a specific bond.

The Maurer et al. and WO 98/33520 references have been discussed supra.

DNA has a net negative charge, whereas proteins have a more positive charge due to the amino terminus. Merriam-Webster's Dictionary defines van der Waals forces as "the relatively weak attractive forces that act on neutral atoms and molecules and that arise because of the electric polarization induced in each of the particles by the presence of other particles" (see page 1306, left column). Davies et al. teach that antigens and antibodies interact through hydrogen bonds at the site of interaction (see the Abstract in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome taught by the WO 98/33520 document to encapsulate the CpG motif taught by the WO 98/37919 document, the antigen/allergen taught by the '126 patent, and the targeting agent taught by Maurer et al. in the method taught by the '126 patent to modulate an immune response away from a Th2 response. Davies et al. and the Merriam-Webster's Dictionary teach that the antigen and factor can interact through van der Waals forces and the antigen and FcRL can interact through hydrogen bonds. Claim 89 is included because placing the antigen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the encapsulated antigen/allergen, CpG motif, and targeting agent to modulate an immune response away from a Th2 response as taught by the WO 98/37919 and WO 98/33520 documents, and Maurer et al. which interact via bonds as taught by Merriam-Webster's Dictionary and Davies et al. in the method taught by the '126 patent because it is a useful treatment modality for Type I allergic diseases as taught by the WO 98/37919 document, the liposome increased the half-life of the antigen (with an added benefit of decreased concentration), and the targeting agent would target the CpG motif and antigen/allergen to the endocytic pathway with a reasonable expectation of success.

26. Claims 160-161, 163-167, and 175 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346).

The '126 patent has been discussed supra.

The '126 patent does not teach the modulation of the immune response away from a Th2 response (i.e. toward a Th1 response) and the generation of a specific set of cytokines (Th1), nor does it use a "factor", such as a CpG motif, with the antigen when exposing the pAPC to said antigen.

Spiegelberg et al. teach that IgE (i.e. Th2) responses are inhibited by allergic gene immunization which is presented by dendritic cells and CpG motif immunostimulatory oligodeoxynucleotides (Th1 inducing agent) (see the entire document). Spiegelberg et al. teach that a form of immunization of allergen gene immunization and CpG motif immunostimulatory oligodeoxynucleoties provides a great advantage over conventional immunotherapy because the allergens are produced in the host's cells and are mainly intracellular; therefore, they would not cause anaphylactic reactions. The gene vaccination resulted in Th1 immune responses which would be contrary (modulate away from) Th2 and IgE antibody responses (see page 93, left column and right column, lines 1-6 in particular). Specifically, the gene vaccination of an allergen induced a Th1 response even in the presence of an ongoing Th2 response (see page 95, right column in particular). The reference further teaches that ISS ODN (CpG oligonucleotides) not only have a stimulatory effect on Th1 cell differentiation, but also a suppressive effect on Th2 cell function in allergic inflammation.

Arthur Krieg teaches that CpG DNA creates a Th1-like cytokine environment (e.g. IL-12, IFN-γ, and TNF-α) and enhances the function of antigen-presenting cells, such as macrophages, monocytes, dendritic cells (i.e. pAPCs), and B cells that have bound specific antigen (allergen) will be preferentially activated by CpG DNA "factor" (see page 343, left column and Figure 1 in particular). Further, "recent experiments have demonstrated that the Th1-like effect of CpG DNA can be used to reverse the T helper-2 (Th2) immune

response to an allergen, preventing disease in a mouse model of asthma" (see page 344, left column, paragraph 2 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of modulating an immune system response to an allergen comprising isolating pAPC, exposing said pAPC to an allergen as taught by the '126 patent and a CpG oligonucleotides (Th1 inducing agent) as taught by Spiegelburg et al. and Krieg, followed by administration of said "exposed" pAPC to a subject, as taught by the '126 patent, in order to specifically direct said immune response away from a Th2 response towards a Th1 response to treat allergic diseases as taught by Spiegelberg et al. and Krieg.

One of ordinary skill in the art would have been motivated to perform said method as treatment for a Th2 mediated pathogenic condition (such as allergy) because a successful specific immunotherapy of allergy is associated with changes from a prevalent Th2 to a prevalent Th1 profile of allergen-reactive Th cells, and such a treatment would cause redirection of an allergic Th2 response towards a Th1 response as taught by Spiegelberg et al., and Krieg with a reasonable expectation of success.

27. Claims 168-169, 185, and 187-190 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346) as applied to claims 160-161, 163-167, and 175 above, and further in view of Maurer et al., of record.

The '126 patent, Spiegelberg et al., and Krieg have been discussed supra.

The combined references do not teach using a targeting agent, such as FcRL.

Maurer et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the targeting agents (i.e. IgG, mannose receptor, and DEC-205) taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent to modulate an immune response away from a Th2 response toward a Th1 response as a method of treating allergy.

One of ordinary skill in the art would have been motivated to use the targeting agents taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent because the targeting agents guide the allergen into the endocytic pathway of dendritic cells to modulate an immune response, such as allergy, for therapeutic purposes with a reasonable expectation of success.

28. Claims 170-173 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346) as applied to claims 160-161, 163-167, and 175 above, and further in view of WO 98/33520 (IDS reference, of record).

The '126 patent, Spiegelberg et al., and Krieg have been discussed supra.

The combined references do not teach using an encapsulating devise.

The WO 98/33520 document has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liposome taught by the WO 98/33520 document to encapsulate the CpG motif and allergen taught by WO Spiegelberg et al. and Krieg and the antigen/allergen taught by the '126 patent in the method taught by the '126 patent to modulate an immune response away from a Th2 response. Claim 89 is included because placing the antigen and factor in separate or the same liposome(s) does not lend any patentable weight because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the encapsulated antigen/allergen and CpG motif to modulate an immune response away from a Th2 response as taught by the Spiegelberg et al. and Krieg document in the method taught by the '126 patent because it is a useful treatment modality for Type I allergic diseases as taught by the Spiegelberg et al. and Krieg, and the liposome increased the half-life of the antigen with an added benefit of decreased concentration with a reasonable expectation of success.

29. Claims 174, 185, and 187-190 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346) as applied to claims 160-161, 163-167, and 175 above, and further in view of Maurer et al., of record, and WO 98/33520 (IDS reference, of record).

The '126 patent, Spiegelberg et al., and Krieg have been discussed supra.

The combined references do not teach using a targeting agent or an encapsulating agent.

The Maurer et al. and WO 98/33520 references have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the targeting agents (i.e. IgG, mannose receptor, and DEC-205) taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in an encapsulating agent as taught by the WO 98/33520 document in the method taught by the '126 patent to modulate an immune response away from a Th2 response toward a Th1 response because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells.

One of ordinary skill in the art would have been motivated to use the targeting agents taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent because the targeting agents guide the allergen into the endocytic

pathway of dendritic cells to modulate an immune response, such as allergy, for therapeutic purposes, and wherein the encapsulation increases uptake of the antigen/allergen by the dendritic cells to modulate an immune response as taught by the '126 patent with a reasonable expectation of success with a reasonable expectation of success.

30. Claim 184 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346) as applied to claims 160-161, 163-167, and 175 above, and further in view of Maurer et al., of record, and Davies et al. (PNAS 1996; 93: 7-12).

The '126 patent, Spiegelberg et al., and Krieg have been discussed supra.

The combined references do not teach that the targeting agent and antigen are associated by a bond.

The Maurer et al. and Davies et al. references have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the targeting agents (i.e. IgG, mannose receptor, and DEC-205) taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent to modulate an immune response away from a Th2 response toward a Th1 response as taught by Spiegelberg et al. and Krieg. Claims 189-190 are included because the entire IgG molecule taught by Maurer et al. is encompassed within the meaning of "at least the Fc portion of an Ig molecule" as recited in claim 189, and "at least the Fc portion of an IgG molecule" as recited in claim 190. It would have further been obvious to one of ordinary skill in the art at the time the invention was made that the IgG and antigen/allergen were acting via hydrogen bonds as taught by Davies et al.

One of ordinary skill in the art would have been motivated to use the targeting agents taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent because the targeting agents guide the allergen into the endocytic pathway of dendritic cells to modulate an immune response, such as allergy, for therapeutic purposes to

modulate an immune response as taught by the '126 patent, Spiegelberg et al., and Krieg with a reasonable expectation of success with a reasonable expectation of success.

31. Claims 184 and 191 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,994,126, of record, in view of Spiegelberg et al. (Allergy, 1998; 53(Suppl. 45): 93-97) or Arthur Krieg (BioDrugs, 1998; 10(5): 341-346) as applied to claims 160-161, 163-167, and 175 above, and further in view of Maurer et al., of record, WO 98/33520 (IDS reference, of record), Davies et al. (PNAS 1996; 93: 7-12), and Merriam-Webster's Dictionary (10th ed. Merriam-Webster, Inc. Springfield, 1996, page 1306).

The '126 patent, Spiegelberg et al., and Krieg have been discussed supra.

The combined references do not teach

The Maurer et al., WO 98/33520, Davies et al., and Merriam-Webster's Dictionary references have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the targeting agents (i.e. IgG, mannose receptor, and DEC-205) taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in an encapsulating agent as taught by the WO 98/33520 document in the method taught by the '126 patent to modulate an immune response away from a Th2 response toward a Th1 response taught by Spiegelberg et al. and Krieg, and because the liposomes are targeted to the same endocytic pathway and the antigen and factor would end up in the same vesicles of the same dendritic cells. It would have further been obvious to one of ordinary skill in the art at the time the invention was made that the IgG and antigen/allergen were acting via hydrogen bonds as taught by Davies et al. and that the antigen and CpG factor were interacting via van der Waals forces. Claims 189-190 are included because the entire IgG molecule taught by Maurer et al. is encompassed within the meaning of "at least the Fc portion of an Ig molecule" as recited in claim 189, and "at least the Fc portion of an IgG molecule" as recited in claim 190.

One of ordinary skill in the art would have been motivated to use the targeting agents taught by Maurer et al. in conjuction with the allergen and CpG oligonucleotides taught by Spiegelberg et al. and Krieg in the method taught by the '126 patent because the targeting agents guide the allergen into the endocytic pathway of dendritic cells to modulate an immune response, such as allergy, for therapeutic purposes, and wherein the encapsulation increases uptake of the antigen/allergen by the dendritic cells to modulate an immune response as taught by the '126 patent with a reasonable expectation of success with a reasonable expectation of success.

32. No claim is allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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